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THE FORMATION AND THE CLINICAL SIGNIFICANCE OF ALBUMIN AND CASTS IN THE URINE.¹

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To understand fully the formation and the significance of casts in the urine necessitates our following the proteid molecule through the body from the time of its absorption to its elimination as a proteid substance, or as one of the more perfect katabolic products of the normal excreta. Accepting the theory that animal life is purely a chemical katabolic process,—one in which the multiplex molecule is constantly being simplified by a process of oxidation,—we have in a measure a simple problem to elucidate. On first thought it may appear difficult to explain the continual upbuilding of the animal kingdom from its conception to the period of its maturity. This is easily accounted for, however, by taking these complex proteid molecules into the system more rapidly than they can be oxidized and eliminated as perfect katabolic products. Consequently, the surplus of multiplex molecules is continually piled up, one upon another, in a mechanical manner, rather than by synthetic formation of the multiplex out of the simple molecules. It is in the imperfect utilization of the proteid molecules that we discover the true source of our casts and albumin found in the urine, as will be more fully elucidated later.

Following the proteids, or true tissue-builders, a little more closely, we find that they all enter the alimentary canal in the form of an alkali-albuminate, either in the

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polymeric state, as found in the vegetable kingdom, or in the "monomeric" form common to the animal fluids and solids. In the alimentary canal the multiplex must be transformed into the simple form. This accomplished, the alkali-albumin is acted upon in the stomach by the hydrochloric acid and isomerically transformed into acid albumin, after which it is further acted upon by the ferment-body, pepsin, and isomerically transmuted into a series of isomers known as albumoses, finally reaching the isomeric state in which it is known as a true peptone, which is the only form, so far as we know at the present time, in which a proteid can be taken up by the epithelial cells of the alimentary canal. Only one-third of the proteids taken in with the foods is so transformed in the stomach, the remaining two-thirds being carried through a similar isomeric transmutation, with the ultimate production of a peptone in the intestinal canal. This change is brought about by the action of the ferment-body, trypsin, secreted by the pancreatic gland, together with the proteolytic ferments of the bile and intestinal secretions. When all the proteids have been converted into this particular isomeric condition, in which they can be drawn into the protoplasmic substance of the epithelial cells, they are absorbed by these special cells. After the peptone has gained access to the protoplasm of these cells, of which there are three distinct sets as regards their function, it is further isomerically transmuted; one set of cells discharging the contained proteid into the entero-hepatic blood-stream as serum-albumin so-called, another as serum-globulin so-called, and a third as fibrinogen so-called. As a rule peptone is not found in the entero-hepatic blood. If the transmuting function of these cells is overtaxed, then the peptone may be discharged as such into the entero-hepatic blood. The peptone being a toxic form of proteid, when it reaches

the hepatic gland the epithelial cells of the liver take up the peptone and transmute it into a non-toxic form, in a manner similar to that of the cells of the intestinal canal when they are performing their function normally; thus arresting the entrance of the peptones into the systemic circulation at large, and thus preventing general toxemia from the peptones.

Having disposed of the peptones, we can direct our attention to the so-called serum-albumin, serum-globulin, and fibrinogen. The reason for questioning these names as referring to a simple substance will be made clear when serum-albumin is discussed in detail in connection with its so-called presence in the urine, and in the formation of casts.

After these proteid bodies have passed into and through the liver, they are taken up by a process of absorption and isomeric transmutation to form the various tissues and glands of the animal economy. Depending upon the isomeric form in which they exist, and the amount of water and inorganic salts with which they are combined, we have formed the various structures of the body. This isomeric condition and transmutation are largely the chemical phenomena that determine the different physical characters and functions of the various organs and structures of the body, all of which can be brought about without the proteid elements undergoing any decided chemical decomposition or oxidation-reduction. If the absorption and isomeric transmutation of a given structure are more rapid than its discharge from the structure into the lymph-channels, then there is the natural growth or hypertrophy of the tissue or organ. If the reverse is true, we have a wasting away or atrophy. A large amount of the proteid is taken up from the blood to supply the growth and functional activity of the epithelial cells constituting the glandular system. Much of this is isomerically dis-

charged to form the ferment-bodies, which should be looked upon in this light as true excretory products. The balance primarily taken into these cells, after having served its isomeric purpose to a given gland, is either isomerically discharged into the lymph-channels, as occurs with the non-epithelial structures; or it is then and there directly oxidized into the katabolic excretory products of the body. The latter is unquestionably largely true. The balance of the proteid not so oxidized passes out of the cells or structures in which it has been serving its purpose, not as the result of oxidation-transmutation, but governed by the law of isomerism. This being true, the proteids of the lymph and blood contain these many isomeric products. It is in this law of isomerism and multiplex formation of proteid bodies that we find justification for questioning the terms serum-albumin, etc. Serum-albumin is not a simple proteid substance, but it is rather a proteid compound made up of many isomeric forms of proteid molecules. Serum-albumin, so-called, is known to be composed of at least three distinct forms of the proteid molecule, and in all probability they can be numbered as legion. At all events, we are justified in the assertion that it is not a simple substance, but is made up of a multiple of isomeric forms of proteid molecules.

Following this isomeric transmutation-theory for the proteid bodies, we are forced to the conviction that oxidation-reduction occurs only in the epithelial cells and not in the muscles, blood, and connective-tissue structures. This is also sustained by the great scarcity of oxidation-products in the blood and the lymph-channels and their overwhelming abundance upon the outside of every glandular organ in the body. Therefore, we assume that after the proteid bodies have served their purpose in this isomeric fashion they come around to the various glandular organs as waste and

excretory products, to be taken up into these cellular structures of the glands, together with oxygen. The oxygen, acting upon this fully utilized proteid material in the protoplasm of these epithelial cells, reduces or oxidizes the proteid substance into the normal katabolic excretory products commonly found in the excreta. This is assuming that the system acts normally.

Viewed in this light, the excretion of this fully utilized proteid unoxidized, but in some of its many isomeric forms, does not cause any direct loss to the system, any more than its elimination as the more perfect products, urea, etc. For these fully utilized proteid substances are of no more value to the physiological economy. When eliminated as such they simply indicate imperfect oxidation in the excretory glands. Whenever, for any reason, the normal action of the system is disturbed, instead of finding in the excreta the katabolic products commonly classed as normal, we find an innumerable number of abnormal or leukomain products, among which are albumin and casts.

This brings us to a point at which we can more intelligently discuss the presence of albumin in the urine, the formation of casts, and the significance to be attached to their presence in the urine.

Taking up, first, the presence of albumin in the urine, we all know that it may come through the kidney itself or from the line of the genito-urinary tract between the renal organs and the external end of the genital tract. As the former source is the only one that concerns us at present, the latter will be wholly omitted in this discussion.

First, it can be asserted, as a well-established chemico-physiological law, that when the digestive function is perfectly performed, absorption and assimilation perfectly accomplished, and with the full quota of oxygen throughout the system, normal katabolic bodies only are

produced. Under these circumstances the epithelial cells of the renal glands will not be overtaxed, the nutritive vitality of the protoplasm will be maintained perfectly, all the utilized proteid bodies will be fully oxidized in these cells into the complete katabolic products, such as urea, etc. Under these circumstances, neither the so-called serum-albumin nor any of the antecedent, derivative or isomeric forms of albumin will be found in the renal excretion.

Special exception is taken to the word "serum-albumin" from the fact that writers upon this subject have commonly stated, and still are stating, that the form of proteid found in the urine is serum-albumin, serum-globulin, peptone or propeptone, chiefly, however, the first. In fact, some go so far as to limit it exclusively to serum-albumin. They state that the albumin reaches the urine through the walls of the capillary blood-vessels which constitute the Malpighian tufts; that it is a filtrate from the blood in the lumen of the blood-vessels into the lumen of the uriniferous tubules.

Under the combined light of our present and advanced chemical, physiologic, pathologic, clinical and therapeutic knowledge—and all these must go hand in hand if accurate deductions are to be drawn—good reason for doubting the common statements that serum-albumin reaches the urine by a simple process of filtration through the walls of the blood-vessels which enter into the formation of the Malpighian tufts, is at once forced upon the scrutinizing mind of the close investigator. Certain it is that serum-albumin, so-called, as a single and distinct form of proteid, does not exist. We are further told by the physiologist that this so-called serum-albumin does not diffuse through an animal membrane. We also know from our pathological investigations that in those forms of renal disease in which there is the largest amount of albumin found in the

urine, the rule is to find the vascular walls unchanged ; and in those instances in which we find the greatest amount of vascular change, as in the cases of extensive capillary fibrosis, we often find little or no albumin. In connection with this last statement we except absolute traumatism, and in part those cases of truly inflammatory changes. In the latter, however, as in the acute exudative inflammation of the kidneys, there is little or no albumin in the urine early in the disease. As the process continues, however, and the epithelial cells become more poorly nourished and are called upon to accomplish an increased amount of excretory work at the same time that their nutritive supply is defective, the renal epithelial cells become swollen and granular and discharge, not serum-albumin so-called, but the various isomeric forms of fully utilized albumin, which the cells are not capable of oxidizing into the complete products, urea, etc. We find further, as a general rule, that the amount of albumin is usually in direct proportion to the amount of retrograde change in the epithelial protoplasm. There is, however, an exception to this rule, which will be explained fully later on in the paper.

The physiological chemists teach that this so-called serum-albumin in the alkaline medium of the blood will coagulate if the temperature is raised above 72° C. (161.6° F.) or, to be more accurate, if the temperature is raised to just 73° C. (163.4° F.) and is maintained at that point, a precipitation of the serum-albumin, so-called, occurs. After this has been filtered out, if the temperature of the filtrate be again raised to just 77° C. (170.6° F.) and maintained at that point for a short time, precipitation of the so-called serum-albumin again occurs. When this is filtered out, if the temperature of the filtrate be again raised to 84° C. (183.2° F.), the so-called serum-albumin is again precipitated.

And these three different proteid bodies deflect the plane of the polariscope to different degrees. Yet they all react to the common tests for the proteids in general. Which of the three is the serum-albumin that resulted from the isomeric transmutation of the peptone in the epithelial cells of the alimentary canal, and was discharged into the entero-hepatic blood, has not been determined. This much we are justified in asserting, viz., that the so-called serum-albumin, as we commonly obtain it from the blood, is *not* a single specific proteid compound. We may go further and assert that it is a very complex proteid compound made up of many isomeric forms of the proteid elements, some of which may be in the form in which they left the epithelial cells of the intestinal wall and unutilized by the system; but most of them are different isomeric forms that have been fully utilized by the structures of the body, isomers that are en route from the various glands and structures of the body to the glandular organs where they are to be taken up, together with oxygen from the blood, and oxidized into the end-products of tissue-waste.

Turning now to our urinary analysis, we find that in the presence of the same salts in the urine as are to be found in the blood, the albumin contained in the urine is not always coagulated by the application of heat. The urine must be acidulated to insure the coagulation of this so-called serum-albumin in the urine. This makes a decided chemical difference in the so-called serum-albumin of the blood and urine. This fact alone helps to establish the theory that the albumin of the urine differs from that commonly known as serum-albumin of the blood. It also aids in sustaining the isomeric transmutation theory as the true explanation for these differences. At times very prolonged boiling is necessary to determine the presence of albumin in the urine; and any one who does much work in this line

cannot avoid noticing the different degrees of heat required and the time of the heat-exposure necessary to produce the coagulation of the albuminous constituents of the urine. Thus we find one contradiction follows another in such rapid succession that doubt is cast upon the whole subject as formerly recorded, and a careful analysis of the evidence upon which these statements are made is demanded. In fact, a new interpretation of the whole subject is required.

"In the amphibia the kidney has a double vascular supply; it receives arterial blood from the renal artery, but there is also poured into it venous blood from another source. The femoral vein divides at the top of the thigh into two branches, one of which runs along the front of the abdomen to meet its fellow in the median line and form the abdominal vein, while the other passes to the outer border of the kidney, and branches in the substance of the organ, forming the so-called renal portal system. Now, the glomeruli are supplied exclusively by the branches of the renal artery, and the renal vena porta only serving to form the capillary plexus around the tubuli uriniferi, where its branches are joined by the efferent vessels of the glomeruli. From this it is obvious that, if the renal artery be tied, the blood is shut off entirely from the glomeruli, and the kidney, by this simple operation, is transformed into an ordinary secreting gland, devoid of any special filtering mechanism; an actual observation of the kidney of the newt has shown that under these circumstances there is no reflux from the capillary network surrounding the tubuli back to the glomeruli. Nussbaum has ingeniously made use of such a kidney to ascertain what substances are excreted by the glomeruli, and what by the tubuli in some other part of its course. He found that sugar, peptone, and albumin, which, injected into the blood, readily pass through the

untouched kidney and appear in the urine, did not pass through a kidney, the renal arteries of which had been tied; these substances, therefore, are excreted by the glomeruli. Urea, on the other hand, injected into the blood, gives rise to a secretion of urine when the renal arteries are tied. This substance, therefore, is secreted by the epithelium of the tubules, and in being so secreted gives rise, at the same time, to a flow of water through the cells into the interior of the tubuli."

Examined superficially, this line of experimentation appears to prove conclusively that the albumin found in the urine is the so-called serum-albumin which has filtered through the walls of the capillary vessels forming the Malpighian tufts. Examined more closely, together with other facts, and as it does not explain how the non-diffusible serum-albumin passes through a non-diffusing membrane; the filtration-theory, which at first appeared to be proved conclusively, becomes very uncertain, if not absolutely disproved.

In view of the fact that serum-albumin so-called is not diffused through an animal membrane, how surcharging the blood with this serum-albumin causes the excess to be filtered through the vascular walls into the uriniferous tubules, or how increasing the quantity of the so-called serum-albumin in the blood causes pathologic changes in the capillary walls, and thus enables them to transmit what they normally do not, has not been explained.

A simple assertion is made, and one which does not meet all the conditions necessary for the perfect explanation of a complete and practical theory.

There can be no question as to the undeniable facts that injecting or surcharging the blood with albumin causes albumin to appear in the urine. Neither can it be denied that ligation-experiments resulted in the finding of albumin in the renal excretion. But the

simple statement of facts does not explain satisfactorily how the non-diffusing membrane so suddenly became one that admitted of the passage of the proteid compound. Neither does it explain the pathological evidence that in those renal lesions where the blood-vessels are not altered, the largest amount of albumin is found in the urine, while with badly damaged blood-vessels, and fairly normal epithelium in the tubules, little or no albumin appears in the renal excretion. The diffusion-theory being untenable, a more rational explanation must be sought, and one which will fully meet all these apparently conflicting phenomena.

A solution of this problem is easily found in a number of ways. First, a superabundance of the proteid bodies in the blood may overtax or exceed the oxygenating capacity of the system and of the renal cells in particular. As a result, the deficiency in oxygen prevents the complete oxidation of the proteid elements into the perfect katabolic bodies, urea, etc.; an isomeric form of albumin is produced, which, together with other imperfect forms of the katabolic series, is excreted by the epithelial cells into the lumen of the uriniferous tubules, giving rise to the presence of varying forms of albumin in the urine. This may occur with or without impairment of the protoplasmic structure of the epithelial cells. This is evidenced by those instances in which the epithelial cells of the kidney excrete albumin in this manner for twenty and thirty years without any disturbance in the functions of the body. The excessive use of starches, sugars, and fats may so exhaust the oxygen-supply that sufficient oxygen is not left in the system to fully oxidize the proteid substances as rapidly as they are taken up from the blood by the renal cells. When this occurs the albumin is discharged unoxidized into the lumen of the uriniferous tubules. The excretion of urea is diminished and the nitrogen contained

in the excreted albumin takes the place of that commonly represented in the larger quantity of urea. So long as the unoxidized proteid substance is that which has not been utilized and is isomerically transformed into a worthless or toxic form, its excretion in this unoxidized form appears to produce little harm to the protoplasmic structures. Similar defective oxidation and excretion of proteid substances frequently follow prolonged and excessive muscular exertion. While the active muscular contractions are being produced, there is a rapid isomeric transmutation and discharge of the proteid bodies from the muscle-structure. At the same time there is a rapid consumption of oxygen in the oxidation of the sugars and fats, to generate the heat required to excite the nervous mechanism into increased activity to produce these rapid metabolic changes. In this manner the blood is surcharged with the fully utilized proteid elements, which in this isomeric form are not especially toxic in their nature. Being taken up by the epithelial cells of the kidney more rapidly than is the oxygen with which to perfectly oxidize these proteid compounds, we find the urine contains a lower percentage of urea than normal, but at the same time there is an excess of uric acid and albumin; so that if all the nitrogen is computed in the urea and albumin, we find there is actually an increased destruction and elimination of the utilized proteids and their katabolic products above what occurs under normal circumstances. This and similar forms of albumin in the urine is never physiological, as has been claimed by some. It is always an indication of an abnormal state of the system and of the renal glands. At the same time it may exist for months and years and never produce the more pronounced degenerative conditions of the renal structures that are generally classed under the common term of "Bright's Disease." On the other hand, if the renal

epithelial cells are called upon to oxidize or excrete the fully utilized proteid compounds, and they are at all toxic in their nature, then the epithelial cells undergo more or less rapid degenerative changes. Then there comes a time when these toxalbumins are neither oxidized nor excreted. Then their retention, varying as they do in kind and toxicity, explains the large variety of toxic symptoms known under the time-honored term "uremia," though never due to the retention of urea as such. Speaking of this class, in which there is an impaired nutritive state, with degenerative changes in the chemical structure of the epithelial cell-protoplasm, the elimination of these isomeric forms of albumin by these degenerated cells explains two facts, viz.: That the quantity of albumin in the urine is always in direct relation to the changes in the epithelial cells and the discharge occurs abundantly when no abnormal changes exist in the walls of the capillary blood-vessels. This statement, of course, excepts also the presence of albumin in the urine resulting from direct traumatism to the renal structure, and in a measure the inflammatory lesions of the kidney, such as the acute exudative or diffuse nephritis. Here the laws common to inflammation in all parts of the body come into play, and the damaged vessels permit, in a measure, the direct escape of the liquor sanguinis, and of the corpuscles as well. Even in these instances, as the pathological lesion progresses, it becomes more and more apparent that the epithelial cells are largely concerned in excreting albumin, as already described.

Further, the elimination of those different isomeric forms of albumin, and not the so-called serum-albumin, easily explains the differences in the reaction of the two albumins. Yet both, and in fact all kinds, obey the common law of responding alike to the tests for the proteid substances in general. Some, it is true, react

more readily than others. This explanation is in perfect accord with chemical and physiological data, and it also is sustained by the clinical and pathological findings, which is not the case with the filtration-theory.

The second part of this experiment, or ligation of the renal artery, cannot be accepted as proving conclusively the filtration-theory, because the experiment in itself establishes at once an abnormal state of the system. Shutting off the blood-supply from the renal glands of necessity at once impairs the functional activity of the excretory epithelium of the kidneys. The katabolic bodies that should be eliminated by the renal epithelium are retained, and the general nutrition is impaired. If these excretory products reach the kidney at all it must be in an abnormal and round-about course. Therefore, the experiment does not prove the filtration-theory, but helps rather to uphold and strengthen the suboxidation and epithelial excretion-theory.

At this point it should be remembered that urea is a very soluble and easily eliminated katabolic body, which is normally cast out of the system by these cells, while the isomeric forms of albumin are, in both instances cited, incomplete and imperfectly formed excretory products; in the one instance taking the place of or in excess of the normal output of urea, yet without special damage to the renal epithelial cell-protoplasm. On the other hand, it is associated with a marked and progressive retrograde change in the protoplasm of the renal epithelial cells. Urea is also a very soluble and easily diffusible substance. Therefore, it is quite easy to understand how it was that urea was quickly detected in the urine when albumin was not, after injecting the two substances into the blood.

Nussbaum's experiment on the artificial production of albuminuria in the frog is exceedingly interesting:

"The renal arteries being tied, and injection of urea (1 cu. cm. of a 10% solution) into the blood gave rise to a flow of urine which was free from albumin. Upon loosening ligatures, so as to re-establish the flow of blood through the glomeruli, the urine at once became albuminous." From this it was argued that "the arrest of circulation through the glomeruli had damaged the capillary walls, and so allowed the passage through them into the interior of the Malpighian capsules of the natural proteids of the blood, which, in a normal condition of the capillaries, cannot effect such a passage. The injury, however, was temporary only; in a short time the capillary walls were restored to health and the urine ceased to be albuminous."

This experiment, like the former, appears to prove conclusively the escape of the albumin by the filtration-theory, but it fails to explain the abundance of albumin in the urine with the condition of the capillaries unchanged and its absence when the blood-vessels are in a pathologic state. The shock of the operation, and the general disturbance of the whole nutritive process in consequence of the operation, the continued excretory activity of the cells while the nutrition was shut out of the kidney, would naturally cause a marked deterioration in the nutritive state of the renal cell-protoplasm. Suddenly readmitting the blood, now overcharged with effete material, still further augments the excretory work imposed upon the renal epithelium, and causes further degeneration, until this isomeric form of albumin is excreted, as before described. This method of explaining the development of the albuminuria is supported by daily observations, both clinical and pathological.

In further support of this line of argument, the acute renal congestions are cited. In these cases of acute congestion the renal circulation is, in some instances,

absolutely arrested and the vascular strain is very great. Uremic symptoms even may be developed, but no albumin appears in the urine so long as the nutritive activity of the epithelial protoplasm is retained; that is, assuming that there is no excessive intake of albumin or other forms of food that would tend to overtax the oxygenating capacity of the system; but just so soon as marked retrograde changes in the epithelium are added to the vascular disturbance, albumin appears in the urine, and the amount of albumin present in the urine is always in direct proportion to the amount of metamorphotic change in the epithelial cells lining the uriniferous tubules.

The same law holds true in cases of chronic congestion of the kidneys, where the condition of retarded renal circulation and overstraining of the capillary vessels may last for months and even years without albumin appearing in the urine; but the moment the epithelial cells commence to retrograde, albumin appears in the urine, and its quantity keeps pace with the amount of damage developed in the excretory cells.

In cases of shock from surgical injury, in which there is no lesion of the blood-vessels in the kidney and in which the circulation is not arrested nor the walls of the vessels overstrained, albumin appears in the urine in large amounts and often is accompanied by casts in abundance.

Post-mortem examination confirms the fact that the vascular structures are not involved, but the epithelial cells lining the uriniferous tubules are always found in varying degrees of retrograde metamorphosis. Clinical cases of this character, especially when supported by post-mortem evidence, argue very strongly in favor of a disturbed oxidation, impaired nutrition with increased work forced upon poorly nourished excretory epithelium, as the most rational method for explaining the

presence of albumin in the urine, except in those cases in which there is an excess of the proteid bodies in the blood or more than there is oxygen to fully oxidize, when the isomeric proteid bodies are excreted by the epithelial cells instead of the final products of proteid oxidation, urea, etc. In these cases there is no marked structural change in the kidneys. We also except the cases of true inflammations of the kidney, as already noted. This hypothesis also obviates the necessity of "diffusing" a non-diffusible form of albumin through an animal membrane, which, normally, will not permit of its passage.

The experiments already alluded to are far more logically explained upon the malnutrition and isomeric-proteid excretory-theory than by the diffusion-plan. This method of explanation fits all the different cases and conditions—the experimental, the clinical, and the pathological. It also satisfies the difference in chemical tests in the two instances between the albumin in the blood and the so-called serum-albumin in the urine.

While there is an apparent decrease in the elimination of nitrogen from the system by the falling off in the quantity of urea, it is easily accounted for by taking into consideration the elimination of the same element with the proteid material carried out of the system. The urea, however, represents the highest and most perfect state of bodily oxidation, while the replacing of the urea by albumin or by any of the other imperfect products of oxidation, indicates simply a deviation from the normal standard or a decided state of sub-oxidation with general malnutrition, the degree of malnutrition depending upon the katabolic product eliminated. So long as the kidneys are able to rid the system of these isomeric proteid bodies under their own form, or as the complete oxidation-products, urea, etc., no toxic symptoms occur. If, for any reason, either

with or without the presence of albumin in the urine, the epithelial cells fail to perform their oxidation or excretory function as here described, and these toxic proteid bodies are retained within the system, the so-called uremic or toxic symptoms will be produced, and death often ensues in this manner without the presence of albumin in the urine.

With all these facts before us, it can be asserted that albumin coming directly from the kidney comes from two sources: transudation through the vascular walls of the capillaries constituting the Malpighian tufts, when the renal organs are the seat of a traumatism or an acute exudative or diffuse nephritis, and as an excretion direct from the excretory epithelium. In the latter instance it may be in connection with marked retrograde changes or it may be without any appreciable degeneration or loss of functional activity of the protoplasm constituting the epithelial cells of the kidney, the isomeric proteid bodies in part replacing the fully formed katabolic products of a perfect oxidation and fully relieving the system of all waste and toxic matter. We have already found that in the true inflammatory lesion, by far the largest percentage of albumin in the urine comes from the retrograde change in the epithelium, just as occurs in the non-inflammatory lesions of the kidney with retrograde changes in the epithelial cells.

Viewed in this light, and having determined positively that the albumin takes its origin in the kidney, its presence must be interpreted in a different manner than formerly was the case. It is not serum-albumin, so-called, that we have to consider, but an innumerable variety of isomeric compounds of the proteid series. Its presence may indicate simply its substitution for urea, the structure of the kidney remaining unimpaired for months or years; it may indicate a transudation

through the walls of the capillary blood-vessels in conjunction with a traumatism or a truly inflammatory lesion. Or, lastly, it may indicate substitution for urea, with marked degenerative changes in the epithelial cells of the kidney. Absence of albumin, on the other hand, must not always be taken as a guarantee that the renal cells are sound; for there are many instances found on record in connection with necropsy-work in which the patients have died toxemic from an inability of the renal cells to eliminate any form of nitrogenous waste; the urine prior to death being free from albumin and most of the katabolic excretory products; but at the post-mortem the kidneys are in an advanced state of retrograde metamorphosis.

This brings us to a point where we can more intelligently consider the formation and the significance of casts in the urine. With this conception of the excretion of the proteid bodies, the methods of forming or producing casts becomes an easy matter. Some one of these many isomeric forms of the proteid bodies is excreted by the protoplasm of the renal epithelial cells into the lumen of the uriniferous tubules. Here it comes in contact with the excreted uric acid, which is probably the chemical agent that tends to cause the solidification or gelatinization of the proteid substances to form the casts. That the acid has much to do in the formation is evidenced by the fact that this form of hyaline casts is especially abundant whenever there is an excessive excretion of the uric acid; not that the acid alone is responsible for their formation, but the condition of suboxidation that produces an excess of uric acid is associated with a surcharging of the blood with both unutilized and utilized proteid bodies. When these proteid bodies are taken up into the epithelial protoplasm, with the oxygen for their oxidation, there is not a sufficient amount of the oxygen to perfectly oxidize

all the proteids into the complete katabolic products, urea, etc. As a natural sequence, a part of the proteid escapes as such with the uric acid into the lumen of the uriniferous tubules, and thus forms the hyaline casts. The uniformity with which hyaline casts are found in the urine when subjected to the centrifuge, leads one to believe that a small amount of these isomeric proteid bodies is almost constantly eliminated by the renal cells as one of the katabolic products of tissue waste. The quantity being so small and in solid form in these hyaline casts, such urine does not, as a rule, give any evidence of the presence of albumin when the common tests are used for the detection of the proteid bodies in solution. In addition to the single hyaline casts, the proteids thus excreted by the epithelial cells of the kidney may be condensed in a fine granular form of cast, and yet there is no positive structural change in the protoplasm of the renal cells.

A third variety of cast may be found which is the same hyaline substance with an occasional renal epithelial cell attached to its surface. This is explained by the fact that even in the most normal state of the renal organs, there is, as in every other portion of the body in which epithelial cells are found, a continual desquamation of the outer layer of the epithelial cells; and the lining of the uriniferous tubules is no exception to this general rule. Therefore we are justified in the statement that casts of the hyaline, finely granular variety, and with an occasional epithelial cell attached to the surface of the hyaline cylinder, and especially when small in diameter, are found at all times in the urine. At the same time they do not indicate the presence of any organic changes in the renal glands. This is especially true when there are no pronounced symptoms of any other kind in conjunction with the presence of the casts. Casts of this character do indicate a slight devia-

tion from the ideal physiologic standard already mentioned; they indicate a slight abnormality in the typical functional activity of the system at large, digestion, absorption, assimilation and oxidation, which is usually due to excesses in eating, drinking, working, etc. If the excess is continued year after year, there must of necessity come a time when the renal glands will undergo active degenerative changes. Fortunately, however, Nature has allowed us a wide latitude in which to indulge these excesses; so much so, that we must not take the simple presence of this particular class of casts in the urine as evidence of the beginning of a renal degeneration, or that it is likely to be developed in the near future.

When active pathologic changes are developed in the renal organs we have the same variety of casts above described. Early in the acute exudative nephritis we find an abundance of leukocytes in addition to these hyaline casts and still little or no albumin. But as the lesion advances, and the epithelial cells degenerate, they excrete a larger and often increasing quantity of albumin. Now casts begin to make their appearance in the urine that are positively indicative of established degenerative changes in the protoplasm constituting the epithelial cells. Instead of finding hyaline, very finely granular, and a hyaline with a renal cell or two attached only, we find that the excreted and condensed proteid cylinders or casts are uniformly granular throughout. This granular appearance may be of the fine or coarse type, and gives the cast the appearance as if something had been added to the primary hyaline cylinder or cast, for it now appears more bulky. That this addition is the result of the breaking down and rapid desquamation of the epithelial cells lining the straight or collecting uriniferous tubules, is evidenced both by pathological observation and by a careful analy-

sis of the casts in the urine. Pathologically, the study of the casts is best determined in the non-inflammatory conditions of the renal glands, or in those forms in which the lesion is simply the result of increased work upon a defective nutritive supply; and it is this same change in the epithelial cells, due to the defective nutritive supply excited by the inflammatory changes, that causes the excessive excretion of albumin by the epithelial cells, and in consequence thereof the abundant formation of the casts in the truly inflammatory lesions. When this stage of degeneration of the epithelial cells has been reached, either with or without inflammation, all the different grades of casts in their various stages of formation can be seen *in situ* in the straight or collecting tubules; and so far as my experience goes, and it has been quite a large one, the casts are always found in the straight or collecting tubules. This is very perfectly illustrated in Fig. 1., which was made from a fresh section of the human kidney very shortly after death. Here we find the hyaline finely and coarsely granular, and the fatty casts most perfectly shown; in fact, almost as plainly as we see them in the urine, a result that can only be obtained by this method of reproduction. A few of the epithelial cells lining the tubules remain *in situ* in fairly good condition, while the remainder are in a more or less advanced condition of retrograde transmutation. In other places the epithelial cells have been entirely destroyed, leaving only the tubes of basement-membrane. Sections of this kind are the undeniable evidence of the seat and method of formation of casts.

Studying these casts further in the urine, we find many samples in which there has been a more rapid and extensive desquamation of the epithelial cells lining the tubules. When this is the case we find cast after cast that is either partially or completely covered over

with the degenerating and desquamating renal cells, still retaining their integrity to a sufficient degree to show under the microscope the distinct outline of each cell and its nucleus. This we call an epithelial cast. When the degeneration has gone still further, and the outlines of the attached epithelial cells can no longer be

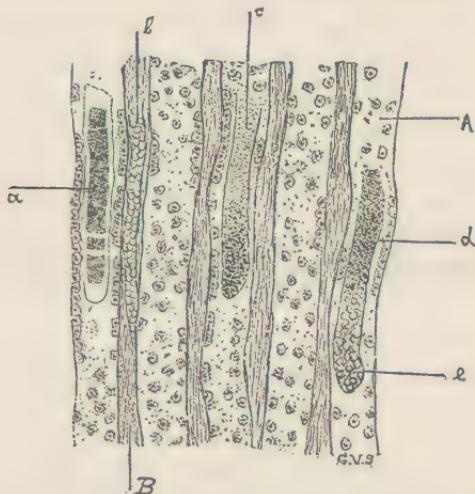


FIG. 1.—Longitudinal section of the pyramidal portion of the kidney illustrating formation of casts in the tubules. $\times 350$. *A*, collecting uriniferous tubule, showing degenerating and desquamating epithelium and a cast in the lumen; *a*, hyaline cast in the lumen of a collecting tubule; *B*, intertubular tissue, thickened by an edematous swelling; *b*, blood-vessel containing blood-corpuscles in the intertubular tissue; *c*, granular cast in the lumen of a collecting tubule; superior extremity finely granular, inferior extremity, or that nearest the apex of the pyramid, coarsely granular; *d*, *e*, cast in tubule; *d*, internal end coarsely granular; *e*, external end in a state of fatty metamorphosis. (Porter, W. H.: "Practical Treatise on Renal Diseases and Urinary Analysis," William Wood & Co.)

recognized, but the nuclei remain visible, we have a nucleated cast. When the degeneration of the epithelial cells has progressed still further, and they are detached from their natural position, and become incorporated with the hyaline substance, we have the finely granular, the coarsely granular, or the fatty cast, depending upon the advance in the degenerative process.

The size of the cast is also a very important factor, the small casts usually indicating an acute or superficial lesion, while the large, coarsely granular and fatty casts are always indicative of an old and well-advanced degenerative lesion of the kidneys.

With a traumatism of the renal organs, and with one form of acute diffuse nephritis, in addition to the casts already described, we have those which are composed of a matting together of the red blood-corpuses, or those composed of the hyaline cylinder covered with the red blood-corpuses, and forming what is known as a blood-cast, a foreign body in the urine that is the only positive evidence that the blood came from the kidneys. It is hardly necessary to say that, microscopically, the cast is a foreign body found in the urine; that it has well-defined and parallel borders; that one end is usually rounded, while the opposite extremity is variously irregular in its outline. At times the cast is more or less twisted upon its long axis, giving it a spiral or cork-screw appearance. This has been explained as being produced by a twirling of the stream of urine as it descends through the tubule. It is better explained by a mechanical distortion of the lumen of the tube, either by an irregular desquamation of the cells lining the basement-tube, or by the irregular development and contraction of the newly formed connective tissue outside and between the tubules, thus distorting the otherwise straight uriniferous tubules that constitute the bundles of Ferrein. If we study the pathological sections carefully, it is in this portion of the kidney, and not in the tubes of the cortical substance, that we find our casts. The so-called waxy cast appears to be nothing more than one of these forms of the hyaline casts which are more opaque than the majority that are found. It is hardly worthy of a separate and distinct classification that can be definitely recognized as such.

In fact, all these hyaline casts vary much in their apparent density, which is probably due to the different isomeric forms of the proteid bodies that enter into their composition and the closeness with which the molecules are packed together; so that as we look at them under the microscope we find that they present a variety of appearances, and do indicate shades of difference in the abnormality of the system.

The presence of peptone, propeptone, etc., in the urine has not been taken up in detail, for as yet no practical tests have been devised for detecting the innumerable isomeric forms of proteids that may be excreted by the renal epithelial cells. Further than this there is no indisputable record that a peptone has ever been found in the urine. In fact, it takes from three to six months to isolate a peptone from a solution, and get it where it can be tested for; therefore, even if it did exist in the urine as such, it would take too long to isolate and test for the peptone to make its detection of any practical value. That there are many different isomeric forms of the proteid bodies to be found in the urine, as excretory products of the renal epithelial cells, can no longer be questioned; but as yet we have no positive method for identifying these with practical ease and certainty.

This much can be said, that anyone following many cases at the bedside, examines many samples of urine and who makes frequent necropsy-examinations, easily learns to differentiate different kinds of proteids in the urine; to recognize early the presence and significance of the casts found in the urine. He soon learns when and where not to condemn the patient as a nephritic subject. He further learns that there are many cases in which there are casts without albumin, and that there are also cases with an abundance of albumin without casts. The latter only occurs where there is

an abundant development of connective tissue at the very apex of the pyramids which contracts the outlet of the tubules and prevents the escape of the casts. This I have seen in a few instances, the sections made from the kidneys after death showing the tubules filled with retained casts. The former, or urine containing casts without albumin, is quite frequent.

The deductions to be drawn from this study are:

1. That serum-albumin as a single proteid substance is a thing of the past.
2. That the epithelium of the uriniferous tubules excretes the various forms of proteid substances that are found in the urine.
3. That it is through this excreted proteid material that our casts are formed.
4. That there are two distinct classes of casts, one denoting no structural change in the renal gland, and one that does indicate positive retrograde changes.
5. That we may find casts and no albumin and vice versa, and that the former is not infrequent.
6. That the one class of casts can be found in almost every sample of urine submitted to the centrifuge.
7. That we are enabled by a close and careful study of the kind and amount of proteid bodies eliminated through the kidney, together with a careful study of the size and character of the casts, to determine the exact condition of the renal glands, and in fact of the system at large.

This much established, the prognosis and treatment become rational and not speculative; and a long and large experience with this class of cases has led me to the belief that a large number of cases are diagnosed as nephritis that have not and may never have the disease. Further, that a large percentage of the cases that actually have renal disease can be not only greatly

improved but actually cured. It, however, can only be accomplished by active treatment applied upon a physiological basis. From a histological standpoint it may be contended they are not cured, but from the physiological they are, just as the man with the fractured leg is never cured histologically, but he practically walks as well as ever and, therefore, functionally is cured.

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